# Aberrant Expression of CD19 and CD43 in a Patient With Therapy-related Acute Myeloid Leukemia and a History of Mantle Cell Lymphoma

*Yen-Chuan Hsieh,[1] Chien-Liang Lin,[2] Chao-Jung Tsao,[2] Pin-Pen Hsieh,[3,4] Ching-Cherng Tzeng,[1] and Shih-Sung Chuang[1,5]*

[1]Department of Pathology, Chi-Mei Medical Center; [2]Division of Hemato-Oncology, Department of Internal Medicine, Lioying Chi-Mei Hospital, Tainan; [3]Department of Pathology, Veterans General Hospital, Kaohsiung; and [4]Center for General Education, Yuh-Ing Junior College of Health Care and Management, Kaohsiung, and [5]Department of Pathology, Taipei Medical University, Taipei, Taiwan.

Mantle cell lymphoma (MCL) is an aggressive B cell lymphoma with frequent involvement of the gastrointestinal tract and peripheral blood (PB). In addition to the B cell markers, the neoplastic cells express CD5 and CD43. In patients with a prior history of MCL with PB involvement, the appearance of leukemic cells after chemotherapy usually heralds a relapse, particularly if the leukemic cells express B cell markers and CD43. We report a patient with MCL who presented with multiple lymphomatous polyposis of the intestine. The staging procedures revealed the involvement of lymph nodes, bone marrow and PB. Three years after chemotherapy, thrombocytopenia with the appearance of rare leukemic cells in the PB was noted. Leukemic cells obtained from bone marrow aspirate expressed CD19 and CD43, suggesting a relapse. Detailed cytomorphological and immunophenotypic studies unveiled the myeloid nature of these leukemic cells, and a diagnosis of therapy-related acute myeloid leukemia was made. This case illustrates the importance of morphologic examination and performing a complete antibody panel in the diagnosis of a suspected relapse in patients with a prior history of lymphoma.

**Key Words:** CD19, CD43, flow cytometry, mantle cell lymphoma, therapy-related acute myeloid leukemia
(*Kaohsiung J Med Sci* 2009;25:389–94)

Mantle cell lymphoma (MCL) is a mature, aggressive B cell lymphoma that usually presents at an advanced stage, with frequent involvement of the peripheral blood (PB) [1,2]. MCL is the most common lymphoma presenting as multiple lymphomatous polyposis of the intestine [3–6]. The neoplastic cells of MCL express CD5, CD20 and CD43, but not CD23 or myeloid antigens [2,7]. In patients with a prior history of MCL, the appearance of leukemic cells usually heralds a relapse, particularly if the leukemic cells express antigens in common with the initial neoplastic cells. CD19 is a membrane protein expressed in B cell neoplasms and in a subset of acute myeloid leukemias (AMLs) [8–10] while CD43 is a leukocyte-specific surface molecule expressed in a variety of hematopoietic cells [11–13].

Received: Feb 6, 2009 Accepted: Apr 6, 2009
Address correspondence and reprint requests to: Dr Shih-Sung Chuang, Department of Pathology, Chi-Mei Medical Center, Tainan, Taiwan.
E-mail: cmh5301@mail.chimei.org.tw

Here, we report a patient who had received combination chemotherapy for MCL and achieved complete remission. Three years later, leukemic cells appeared in the PB, and a relapsed MCL was suspected. Interestingly, flow cytometric immunophenotyping revealed that these leukemic cells expressed CD19 and CD43, but not CD5 or CD20. Further studies revealed the myeloid characteristics of these leukemic cells, indicating therapy-related acute myeloid leukemia (t-AML). This case illustrates the importance of morphologic examination and detailed immunophenotyping in the diagnosis of hematologic neoplasms.

## Case Presentation

### *Clinical history*

A 52-year-old male presented with small intestinal intussusception and underwent segmental resection in March 2005. Peripheral blood involvement (white blood cell [WBC] count, $19.4 \times 10^3/\mu L$; 74% lymphocytes) was noted at the time and a mature B cell lymphoma was confirmed by flow cytometric immunophenotyping. Biopsies of the left inguinal lymph node and bone marrow revealed involvement of lymphoma. Because of the diagnosis of stage IV disease, the patient received four courses of chemotherapy with hyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine and methotrexate) from March to October, 2005, and achieved complete remission. However, thrombocytopenia appeared in late May 2008 (hemoglobin, 12.2 g/dL; WBC count, $3.4 \times 10^3/\mu L$; platelet count, $78 \times 10^3/\mu L$), 37 months after chemotherapy. The platelet count further decreased to $19 \times 10^3/\mu L$ with appearance of rare blasts in early July 2008 (WBC count, $3.4 \times 10^3/\mu L$; blasts, 2%; platelet count, $19 \times 10^3/\mu L$). To confirm the diagnosis of recurrent MCL, bone marrow aspiration and biopsy were performed.

### *Pathology and flow cytometric findings*

The resected small intestine was 15 cm long, and five larger polyps (up to 2 cm in diameter) and numerous smaller polyps were identified in the segment. Microscopically, the tumor cells in the intestine were intermediate in size with moderate nuclear pleomorphism, irregular nuclear contours, and inconspicuous nucleoli. Immunophenotypically, these lymphoma cells expressed CD5, CD20, CD43, IgD, IgM, bcl-2 and cyclin D1, but did not express CD3, CD10, CD23 or bcl-6. The proliferation index, as determined by Ki-67 staining, was 20%. Two of the three mesenteric lymph nodes were involved by lymphoma. Biopsy of the left inguinal lymph node revealed total architectural effacement with a nodular growth pattern. The tumor cells were identical to those in the small intestinal tumor in terms of histopathology and immunophenotype. The PB lymphoma cells, at presentation in March 2005, were small to medium-sized atypical lymphocytes with a dense chromatin pattern and irregular nuclear contours (so-called buttock cells) (Figure A). Flow cytometric immunophenotyping showed that these leukemic cells expressed CD5, CD19, CD20, CD38 and CD43 with a monotypic expression of surface kappa light chain. They were negative for CD10, CD13, CD23, CD33, CD34, CD117 and lambda light chain. Therefore, diagnosis of a stage IV MCL with PB involvement was made.

Three years later, in July 2008, leukemic cells appeared in the PB and relapsed MCL was suspected. Microscopically, these leukemic cells were medium-sized with a fine chromatin pattern and one-to-two nucleoli (Figure B). The percentage of blasts in the bone marrow was 61%, with maturation of myeloid cells. Flow cytometry immunophenotyping of these blasts revealed expression of CD19 and CD43, but not CD5 or CD20. Because the chromatin pattern of these blasts was fine, blastoid transformation of MCL or therapy-related acute leukemia was suspected. Additional immunophenotyping revealed that these blasts expressed CD13, CD33, CD34 (subset), HLA-DR, CD117 and cytoplasmic myeloperoxidase. Cytochemical staining of the bone marrow aspirate showed that the blasts were positive for myeloperoxidase but negative for nonspecific esterase. A cytogenetic study revealed 45,X, t(1;3)(q21;p21), der(7)t(5;7)(q22;p22) [cp8]/45-46; XY [cp12]. These findings confirmed the diagnosis of AML and excluded the differential diagnosis of recurrent MCL.

## Discussion

Flow cytometry is a very useful tool for immunophenotyping. However, an incomplete antibody panel might lead to confusing data and erroneous diagnosis. In our case, because of the presence of leukemic cells expressing CD19 and CD43 and the patient's

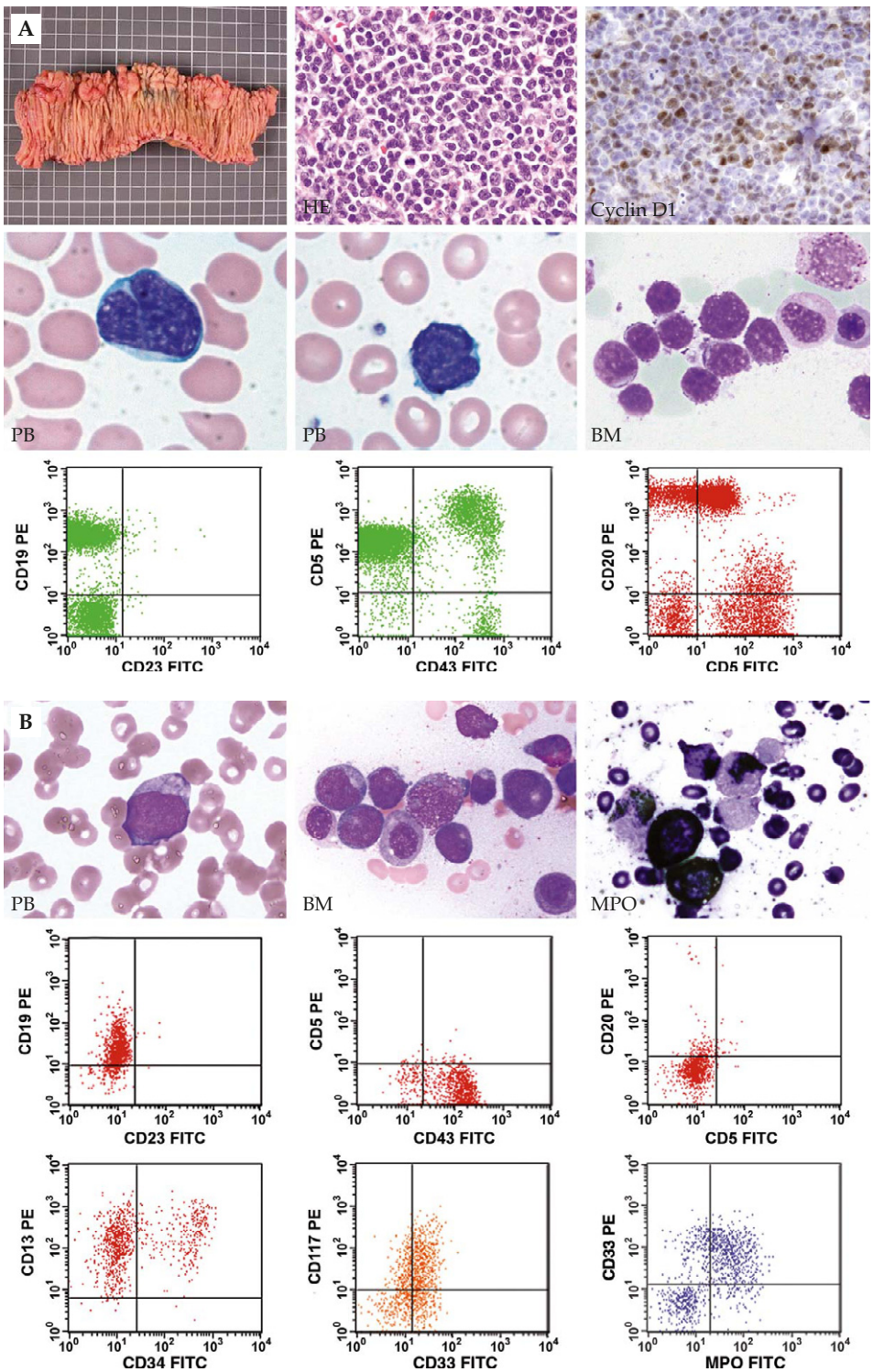


**Figure.** *(A) Mantle cell lymphoma of the small intestine at diagnosis in March 2005 shows multiple lymphomatous polyposes. Microscopically, the lymphoma cells are medium-sized with moderate pleomorphism and irregular nuclear contours (hematoxylin & eosin stain). Immunohistochemically, the tumor cells express cyclin D1. The lymphoma cells in the peripheral blood (PB) exhibit irregular nuclear contours and condensed chromatin (so-called buttock cells). Flow cytometric immunophenotyping of the leukemic cells in the PB revealed expression of CD5, CD19, CD20 and CD43, but not CD23. (B) Therapy-related acute myeloid leukemia diagnosed in July 2008. The leukemic cells in the PB and bone marrow exhibit a fine chromatin pattern and nucleoli, and are positive for myeloperoxidase by cytochemical stain. Flow cytometry shows that, in addition to CD19 and CD43, the leukemic cells express CD13, CD33, CD34 (subset), CD117 and cytoplasmic myeloperoxidase, but not CD5 or CD20.*

history of MCL, recurrent MCL is a reasonable diagnosis. However, the absence of CD5 and CD20 expression strongly argues against this diagnosis because the tumor cells in cases of MCL are mature B cells that express CD20 and the majority of them express CD5. After re-evaluation of the cellular morphology (fine chromatin pattern with nucleoli) and the addition of a myeloid panel, we determined that the leukemic cells expressed myeloid makers (CD13, CD33, and myeloperoxidase), CD34, CD117 and HLA-DR and confirmed the myeloid characteristics of these leukemic cells.

CD19 is a 95-kDa glycosylated, type I integral membrane protein and is expressed by mature and immature B cell neoplasms, benign plasma cells, very rare plasma cell neoplasms and a subset of AML, which is usually associated with t(8;21) [8–10]. In our previous study of AML in Taiwan, the blasts in five (4.5%) of 111 cases expressed CD19 [14]. All five CD19-positive tumors were classified as FAB AML-M2, and four carried chromosomal translocation t(8;21). The t-AML in this current case was also classified as AML-M2, but without t(8;21).

CD43 is a leukocyte-specific surface molecule, which plays an important role in both cell adhesion and signal transduction. It is expressed in virtually all cases of mature T cell and NK cell lymphoma, the majority of MCLs, small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), acute leukemia (myeloid and lymphoid), myeloid sarcoma and mast cell neoplasm, and by 50% of plasma cell neoplasms [11–13]. CD43 is most useful in the differential diagnoses of small B cell lymphoproliferative disorders including SLL/CLL, MCL, marginal zone lymphoma and follicular lymphoma. Because CD43 is rarely expressed in non-hematopoietic neoplasms, it is also useful in differentiating between undifferentiated or anaplastic malignancies (hematopoietic versus non-hematopoietic) [10]. However, because of its frequent expression in various types of hematopoietic neoplasms, CD43 is not lineage-specific and is not included in the routine antibody panels for the immunophenotyping of AML [8,9].

Secondary AML or t-AML arises as a late complication of cytotoxic chemotherapy and/or radiation therapy [15]. Although these patients may be diagnosed morphologically as therapy-related myelodysplastic syndrome (t-MDS), t-AML or t-MDS and myeloproliferative neoplasms (t-MDS/MPN), all of these therapy-related neoplasms should be considered together as a unique clinical syndrome [15]. Two sets of t-AML/t-MDS and t-MDS/MPN are generally recognized by the causative agents [15]. The most common category that occurs 5–10 years after exposure to alkylating agent/radiation is commonly associated with unbalanced loss of genetic materials, often involving chromosome 5 and/or 7. The less common category, which affects approximately 20–30% of cases, occurs 1–5 years after exposure to a topoisomerase II inhibitor and is often associated with balanced chromosomal translocation. However, in practice, many patients have received polychemotherapy that includes both classes of drugs and the boundary between the two categories is blurred. For example, our patient had been treated with both an alkylating agent (cyclophosphamide) and a topoisomerase II inhibitor (doxorubicin). The relatively short interval (3 years) for developing t-AML was in favor of the effects of the topoisomerase II inhibitor, while the cytogenetic findings with aberrations involving chromosomes 5 and 7 were consistent with those of an alkylating agent. This is an example of the blurred boundary between the two categories of causative agents for therapy-related myeloid neoplasms. In conclusion, this case illustrates the importance of morphologic examination and performing a complete antibody panel in the diagnosis of a suspected relapse in patients with a prior history of hematopoietic neoplasms.

## References


1. Campo E, Raffeld M, Jaffe ES. Mantle-cell lymphoma. *Semin Hematol* 1999;36:115–27.
2. Swerdlow SH, Campo E, Seto M, et al. Mantle cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press, 2008: 229–32.
3. Isaacson PG, MacLennan KA, Subbuswamy SG. Multiple lymphomatous polyposis of the gastrointestinal tract. *Histopathology* 1984;8:641–56.
4. O'Brian DS, Kennedy MJ, Daly PA, et al. Multiple lymphomatous polyposis of the gastrointestinal tract. A clinicopathologically distinctive form of non-Hodgkin's lymphoma of B-cell centrocytic type. *Am J Surg Pathol* 1989;13:691–9.
5. Ruskone-Fourmestraux A, Delmer A, Lavergne A, et al. Multiple lymphomatous polyposis of the gastrointestinal tract: prospective clinicopathologic study of 31 cases.

Groupe D'etude des Lymphomes Digestifs. *Gastroenterology* 1997;112:7–16.
6. Kodama T, Ohshima K, Nomura K, et al. Lymphomatous polyposis of the gastrointestinal tract, including mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma. *Histopathology* 2005;47:467–78.
7. Chuang SS, Huang WT, Hsieh PP, et al. Mantle cell lymphoma in Taiwan: clinicopathological and molecular study of 21 cases including one cyclin D1-negative tumor expressing cyclin D2. *Pathol Int* 2006; 56:440–8.
8. Khalidi HS, Medeiros LJ, Chang KL, et al. The immunophenotype of adult acute myeloid leukemia: high frequency of lymphoid antigen expression and comparison of immunophenotype, French-American-British classification, and karyotypic abnormalities. *Am J Clin Pathol* 1998;109:211–20.
9. Kaleem Z, Crawford E, Pathan MH, et al. Flow cytometric analysis of acute leukemias. Diagnostic utility and critical analysis of data. *Arch Pathol Lab Med* 2003; 127:42–8.
10. Gorczyca W. *Flow Cytometry in Neoplastic Hematology. Morphologic-immunophenotypic Correlation*. London: Informa UK Ltd., 2006.
11. Arber DA, Jenkins KA. Paraffin section immunophenotyping of acute leukemias in bone marrow specimens. *Am J Clin Pathol* 1996;106:462–8.
12. Lai R, Weiss LM, Chang KL, et al. Frequency of CD43 expression in non-Hodgkin lymphoma. A survey of 742 cases and further characterization of rare CD43+ follicular lymphomas. *Am J Clin Pathol* 1999;111:488–94.
13. Chu PG, Chang KL, Arber DA, et al. Immunophenotyping of hematopoietic neoplasms. *Semin Diagn Pathol* 2000;17:236–56.
14. Chen SW, Li CF, Chuang SS, et al. Aberrant co-expression of CD19 and CD56 as surrogate markers of acute myeloid leukemias with t(8;21) in Taiwan. *Int J Lab Hematol* 2008;30:133–8.
15. Vardiman JW, Arber DA, Brunning RD, et al. Therapy-related myeloid neoplasms. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press, 2008:229–32.

# 有套細胞淋巴瘤病史的病人得到化療相關性急性骨髓性白血病於週邊血液出現同時表現 CD19 及 CD43 的血癌細胞

謝炎娟[1] 林建良[2] 曹朝榮[2] 謝品本[3,4] 曾慶誠[1] 莊世松[1,5]

[1]奇美醫院 病理部

[2]柳營奇美醫院 血液腫瘤科

[3]高雄榮民總醫院 病理檢驗部

[4]育英醫護管理專科學校通識教育中心

[5]台北醫學大學 病理學科

套細胞淋巴癌是一種惡性度高的 B 細胞淋巴瘤。此種淋巴瘤容易侵犯到消化道及週邊血液。除 B 細胞標記外，這些淋巴瘤細胞同時也表現 CD5 及 CD43。若病人有套細胞瘤侵犯週邊血液的病史，化療之後週邊血液再度出現不正常的白血球，通常意味著淋巴瘤復發，尤其是當這些不正常白血球細胞同時表現 B 細胞標記及 CD43 時。在此我們報告一例腸胃道套細胞淋巴瘤的病例。此病人除腸道外，淋巴結，骨髓及週邊血液也受到淋巴瘤侵犯。在化療後 3 年，此病人有血小板低下的情形產生，並且在週邊血液中出現不正常白血球。另外病人的骨髓中也出現不正常的白血球，這些白血球同時表現 CD19 及 CD43，極可能意味著疾病的復發。但進一步的形態學檢查及流體細胞計數儀免疫型分析，卻有不同的發現。最後我們診斷為化療引起的急性骨髓性白血病。這一例特殊病例告訴我們在遇到具有淋巴瘤病史的病人時，完整形態學及免疫型分析可以幫助我們鑑別是為疾病復發或是另一個疾病的產生。

**關鍵詞：CD19，CD43，流體細胞計數儀，套細胞淋巴癌，治療相關性急性骨髓性白血病**

**( 高雄醫誌 2009;25:389–94)**

收文日期：98 年 2 月 6 日
接受刊載：98 年 4 月 6 日
通訊作者：莊世松醫師
奇美醫院病理部
71004 臺南縣永康市中華路 901 號